77. (Amended) The composition of claim 1 [76], wherein said cells produce [vectors are] filamentous bacteriophage.

REMARKS

For the Examiner's convenience, a copy of the pending claims, prior to entry of the present amendments, is provided as Exhibit A.

Claims 1-33 and 66-81 are pending. Claims 7, 8, 22, 26, 31, 32 and 77 have been amended above. The amendments have been made for clarity and to provide appropriate antecedent basis. The amendments are supported throughout the specification and by the claims as originally filed. Accordingly, the amendments do not introduce new matter and entry thereof is respectfully requested.

Claims 6, 9-15 and 78-81 have been canceled without prejudice. Following entry of the amendments, claims 1-5, 7, 8, 16-33 and 66-77 will be under consideration.

The Office Action alleges that the application is directed to two distinct and independent inventions, as set forth below.

Group I: Claims 1-8, 16-33 and 76-81, directed to a plurality of expression vectors, a cloning system for making these vectors, and the cells transformed therewith.

Group II: Claims 9-15 and 66-75, directed to a vector and a kit for the preparation of vectors encoding heteromeric receptors.

Election of one of the inventions is required under 35 U.S.C. § 121. Although the restriction requirement is traversed for the reasons discussed below, Applicant elects the claims set forth in Group I, claims 1-8, 16-33 and 76-81, for examination.

In the Office Action mailed January 21, 1997, the claims now indicated to be directed to two distinct inventions were indicated to be directed to a single invention classified in Class 435, subclass 69.1. In the subsequent Office Action, mailed June 2, 1997, these claims were examined together. Applicant submits, therefore, that examination of the claims of Groups I and II together has not presented an undue burden on the Examiner. In light of these remarks, Applicant respectfully requests that the Examiner reconsider this second restriction requirement and rejoin the claims of Groups I and II.

Rejections under 35 U.S.C. § 101

Claims 1, 3-5 and 80 stand rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. The Office Action states that as currently used in the art, the term "fusion protein" would include any protein encoded by a member of the immunoglobulin gene superfamily and, therefore, the claims

encompass a population of T or B lymphocytes as they occur in a mammalian system.

Applicant respectfully submits that one skilled in the art understands that the term "fusion protein" does not include naturally occurring gene linkages, such as those that occur during immunoglobulin gene rearrangement in the normal maturation of lymphocytes. The term "fusion protein," as used in the art, specifically refers to an operative linkage between two coding sequences that normally are not linked. The term is used, for example, to describe a protein encoded by a hybrid gene in which part of the coding sequence of one gene is fused with the coding sequence of another gene for a different protein, such as a detectable marker protein. As evidence to support Applicant's assertions as to the use of this term, attached as Exhibit B is R. Meyers, ed., Molecular Biology and Biotechnology: A Comprehensive Desk Reference, p. 479 (1995), which defines a fusion protein consistent with the above assertions and the teachings within the specification.

The use of the term "fusion protein" in the claims and as described in the specification is consistent with its meaning in the art. For example, the specification teaches that a fusion protein can be, for example, a fusion between a subunit of a heteromeric receptor and a bacteriophage coat protein (page 7, lines 10-12). Therefore, given the teachings in the specification and the meaning of the term as it is used in the art, one skilled in the art would know that naturally occurring immunoglobulin genes are not encompassed by the term "fusion protein" and that the claimed invention does not include

lymphocytes as they occur in a mammalian system. Accordingly, Applicant respectfully requests that rejection of claims 1, 3-5 and 80 under 35 U.S.C. § 101 be removed.

Claims 6-8 stand rejected under 35 U.S.C. § 101 as allegedly directed to a non-functional invention due to the plurality of cells being required to produce bacteriophage without limiting the cells to bacterial cells. Although Applicant maintains that the invention is functional as claimed, the claims have been amended above as follows. Claim 77 has been amended to indicate that the prokaryotic cells of claim 76 produce filamentous bacteriophage. Claim 6 has been canceled, and claims 7 and 8 have been amended to depend on claim 77. Therefore, Applicant contends that the claims are directed to a functional invention and respectfully requests that rejection of claims 6-8 under 35 U.S.C. § 101 be removed.

Double patenting rejections

Claims 1-33 and 68-75 stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-33 and 68-75 of copending application serial number 08/470,297. Claims 1-8 and 16-33 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-8, 16-21 and 23-33 of copending application serial number 08/349,131. Applicant respectfully requests that these provisional grounds of rejection be deferred until there is an indication of allowable subject matter.

Rejections under 35 U.S.C. 112, first and second paragraphs

Claims 1-33 and 66-81 stand rejected under 35 U.S.C. § 112, first and second paragraphs, as allegedly lacking enablement. The Office Action states that the claims are incomplete for omitting elements that are allegedly essential to the practice of the invention. Applicant respectfully traverses the rejection for the reasons that follow. Applicant's remarks will address the rejection as it applies to each independent claim.

Claim 1 is directed to a plurality of cells containing diverse combinations of first and second DNA sequences encoding first and second polypeptides which form heteromeric receptors, where one or both of the polypeptides are expressed as fusion proteins on the surface of a cell. Applicants contend that the elements recited in claim 1 are sufficient to point out and claim that which Applicant regards as the invention and, furthermore, that the claimed invention is enabled by the specification. More specifically, claim 1 recites a plurality of cells containing DNA sequences. The specification teaches, for example, on page 6, lines 24-28, that the cells of the invention can be procaryotic cells such as *E. coli*, or yeast or other eucaryotic cells such as mammalian cells, depending on the need. Claim 1 also recites diverse combinations of first and second DNA sequences encoding first and second polypeptides that form heteromeric receptors. The specification teaches on page 6, lines 18-24, how to prepare DNA sequences encoding heteromeric receptor subunits using known methods such as cDNA synthesis and polymerase chain reaction. An

example of preparing diverse combinations of first and second DNA sequences encoding antibody heavy and light chains is described on page 13, line 11, to page 19, line 22. Claim 1 further recites that one or both polypeptides are expressed as fusion proteins on the surface of a cell, as is taught on page 4, lines 19-21. An example of the construction of DNA sequences as fusion proteins for the expression of a polypeptide on the surface of a cell is provided on page 19, line 23, to page 35, line 21. Therefore, in view of the guidance provided in the specification, Applicant contends that the elements recited in claim 1 are sufficient to practice the invention as claimed.

Claims 9-15 have been canceled without prejudice. Therefore, this ground of rejection as it applies to claims 9-15 is now moot.

Claim 16 is directed to a cloning system for the coexpression of two or more DNA sequences encoding polypeptides which form a heteromeric receptor. Applicants contend that the elements recited in claim 16 are sufficient to point out and claim that which Applicant regards as the invention and, furthermore, that the claimed invention is enabled by the specification. More specifically, claim 16 recites that the first and second set of vectors of the cloning system each has a diverse population of DNA sequences contained in a cloning site. The specification teaches, for example, on page 7, line 28, to page 8, line 16, how to prepare a diverse population of DNA sequences and how to anneal such sequences into a cloning site of a vector by methods known in the art. Claim 16 also recites that the first and second vectors of the cloning system have two pairs

of restriction sites symmetrically oriented about a cloning site so as to allow only the operational combination of vector sequences containing the first and second DNA sequences. The specification teaches, for example, on page 9, lines 29-32, that such an orientation of the two pairs of restriction sites allows the vector portions containing the sequences that are expressed to be exactly combined into a single vector. An example of such an orientation is provided in Figure 1. The specification also teaches how to operatively combine the vector sequences for the coexpression of the first and second polypeptides. For example, the specification describes on page 10, line 31, to page 11, line 3, that the first and second vectors can be restricted at the recited restriction sites, digested with a 3' to 5' exonuclease, mixed and annealed. Therefore, in view of the guidance provided in the specification, Applicant contends that the elements recited in claim 16 are sufficient to practice the invention as claimed.

Claim 26 is directed to a plurality of expression vectors. Applicants contend that the elements recited in claim 26 are sufficient to point out and claim that which Applicant regards as the invention and, furthermore, that the claimed invention is enabled by the specification. More specifically, claim 26 recites that the expression vectors contain a plurality of first and second DNA sequences encoding a plurality of first and second polypeptides which form a plurality of heteromeric receptors. As described above, the specification teaches how to prepare expression vectors containing a plurality of first and second DNA sequences encoding heteromeric receptor subunits. Claim 26 also recites that one or more of the receptors exhibits

binding activity toward a preselected molecule. The specification teaches, for example, on page 12, lines 29-33, how to determine whether a heteromeric receptor exhibits binding activity toward a preselected molecule, using affinity procedures such as panning, affinity chromatography and solid phase blotting procedures. Claim 26 further recites that the DNA sequence encoding heteromeric receptors is operatively linked to genes encoding surface proteins. The specification teaches, for example, on page 8, lines 17-20, how to operatively link a DNA sequence encoding a polypeptide to a gene encoding a surface protein by providing the gene encoding the surface protein in frame with the cloning site. Therefore, in view of the guidance provided in the specification, Applicant contends that the elements recited in claim 26 are sufficient to practice the invention as claimed.

Claims 66 and 71 are directed to vectors containing two copies of a gene encoding a filamentous bacteriophage coat protein. Applicant contends that the elements recited in claims 66 and 71 are sufficient to practice the invention as claimed in view of the teachings in the specification. More specifically, claims 66 and 71 recite that one copy of the gene encoding a filamentous bacteriophage coat protein is capable of being operationally linked to a DNA sequence encoding a polypeptide of a heteromeric receptor. As described above, the specification teaches that such a vector can include one copy of a surface protein in frame with the cloning site that contains a DNA sequence encoding a polypeptide of a heteromeric receptor. Claims 66 and 71 also recite that the DNA sequence can be expressed as a fusion protein on the surface of the bacteriophage

or as a soluble polypeptide. The specification teaches, for example, on page 9, lines 10-16, that such expression can be obtained by unlinking peptide expression from surface expression, using, for example, suppressible stop codons or other molecular switches, such as inducible repressor elements. Claim 71 further recites that the vector contains sequences necessary for the coexpression of two or more inserted DNA sequences. The specification teaches, for example, on page 5, line 35, to page 6, line 3, that expression elements include sequences necessary for the transcription, translation, regulation and sorting of the expressed polypeptides. An example of a vector containing sequences necessary for the coexpression of two or more inserted DNA sequences is provided by the vector shown as SEQ ID NO:5 (page 40, lines 3-10). Therefore, in view of the guidance provided in the specification, Applicant contends that the elements recited in claims 66 and 71 are sufficient to practice the invention as claimed.

Claims 80 and 81 have been canceled as redundant with claims 1 and 26, respectively.

The Office Action states that the instant specification discloses the construction and use of the specific pair of expression vectors illustrated in Figure 1, and alleges that the exemplified pair of vectors can be employed in a method of obtaining the incorporation of two different proteins into a single chimeric protein through an efficient mechanism of gene fusion and the expression of that chimeric protein on the surface of a host. Furthermore, the Office Action states that there is no guidance in the specification to permit an artisan to practice

the invention outside of the context of filamentous bacteriophage.

Applicant contends that the specific pair of bacteriophage expression vectors referred to in the Office Action is indicated in the specification to be one embodiment of the invention. The specification discloses that the method can be practiced in any compatible system. Such systems include, for example, plasmids or phagemids in procaryotes such as E. coli, yeast systems and other eukaryotic systems such as mammalian cells. In one embodiment, the DNA sequences are cloned in filamentous bacteriophage vectors (page 6, lines 24-30). Therefore, given the teachings in the specification, one skilled in the art could practice the invention outside of the context of filamentous bacteriophage.

Applicant respectfully points out that the "two different proteins of the heteromeric receptors of the invention" are not, as alleged in the Office Action, either "incorporated into a single chimeric protein" or "fused," and need not be expressed on the surface of a host. The invention provides for the coexpression of two or more nucleic acid sequences expressed as separate polypeptides, such as two subunits of a heteromeric receptor. The first and second vectors are operatively combined such that portions containing the DNA sequences encoding the two subunits are present in a single combined vector. This vector, upon introduction into an appropriate host cell, directs the coexpression of the two subunit sequences. In a specific example, the two coexpressed subunits are assembled on the host surface to form a functional heteromeric receptor (see, for

example, page 4, line 28, to page 5, line 13; page 10, lines 21-30; and Example I, pages 13-36). However, the specification teaches that, depending on the need and the vector/host system employed, the coexpressed polypeptides can also be expressed and assembled in soluble or secreted form (page 6, lines 32-34).

The Office Action states that the first and second vectors of the invention require more than the "two pairs of restriction sites symmetrically oriented about a cloning site and in an identical orientation" alleged to be the only material limitation in the claims. The Office Action continues, "[e]ach of claims 1, 80, and 81, for example, essentially recite nothing more than a desired conclusion without reciting those material elements needed to achieve that conclusion."

Applicant respectfully points out that claims 1, 80 and 81 do not recite the indicated phrase pertaining to first and second vectors and restriction sites. Claims 80 and 81 have been canceled as redundant with claims 1 and 26, respectively. As described above, Applicant submits that claims 1 and 26 are complete as written and enabled by the specification.

In the context of a filamentous bacteriophage, the Office Action asserts that the specification teaches that neither vector should have the ability to produce a viable bacteriophage unless it has been combined with the second vector if they are to be used as described in the instant invention. Applicant contends that the specification teaches operable expression vectors where the two vectors are combined, or, if desired, prior to operative combination, individual vectors which are themselves

operable. For example, as described on page 29, line 22, to page 32, line 21, libraries of viable bacteriophage encoding Hc and Lc polypeptides were independently constructed in the two bacteriophage vectors exemplified in the specification. The DNA from the first vector population was isolated, digested and ligated with DNA from the second vector population, similarly prepared, and the operatively combined vectors were introduced into cells for the coexpression of heteromeric receptor subunits and their assembly as heteromeric receptors. Therefore, Applicants contend that claims directed specifically to bacteriophage vectors need not include a limitation regarding viability.

The Office Action states that the specification is only enabling for the production of single chain binding antibodies, each consisting of a single fusion protein comprising an antibody variable light chain, an antibody variable heavy chain and a surface protein from a host cell. The specification is alleged to lack adequate guidance in the production of a cell or phage which expresses a first and second polypeptide separately. Furthermore, the Office Action states that the novelty of the invention is the provision of a two-vector system which permits the efficient incorporation of DNAs encoding a single variable light chain and a single variable heavy chain into an expression system in which the DNAs are incorporated at random from a population of DNAs encoding different variable heavy and variable light chains. The Office Action also alleges that these DNAs are invariably expressed as single chain antibodies that are initially fused to a surface protein of the host producing them.

It is alleged that the material limitations which provide the novel aspects of the invention should be reflected in the claims.

Applicant contends that the claims are directed to the expression of two independent polypeptides that assemble to form a heteromeric receptor, and that the specification adequately enables the claims. For example, the system described in Example 1 (see Figure 1) provides for the production of cells and vectors that express a first and second polypeptide as separate translation products from a dicistronic transcript. The Hc polypeptide is expressed as a fusion with a filamentous bacteriophage coat protein that directs expression to the cell surface. The Lc is expressed as a separate polypeptide that assembles with the Hc-coat protein fusion on the surface of the cell to form a functional Fab. As will be described further below, the invention can also be practiced with first and second DNA sequences encoding first and second polypeptides that form heteromeric receptors other than antibodies and antibody fragments. Therefore, Applicant respectfully submits that the specification teaches one skilled in the art to coexpress first and second DNA sequences encoding first and second polypeptides which form heteromeric receptors, as claimed.

Furthermore, Applicant contends that the claims recite the necessary elements that provide the novel aspects of the invention. For example, claim 1 recites that the diverse combination of first and second DNA sequences encode first and second polypeptides which form heteromeric receptors. The claimed invention, in which a first and a second polypeptide are expressed, is therefore distinct from single chain binding

antibodies, which consist of a single polypeptide chain. The distinctions between the claimed invention and single chain antibodies will be discussed further below in response to rejections under 35 U.S.C. § 103.

The Office Action further alleges that the specification lacks adequate description of a method of obtaining the expression of a polypeptide on the surface of a host without providing two copies of a gene encoding the surface protein. The first, non-chimeric copy is allegedly essential to the structural integrity of the bacteriophage host and the second copy is allegedly employed to obtain the surface display of the heterologous protein.

The specification teaches that for expression of a polypeptide as a fusion with a surface protein, only a single copy of a gene encoding a surface protein is necessary. For example, in the bacteriophage vectors exemplified in the specification, the non-chimeric copy of the surface protein is taught to be a feature which can be included to reduce the possibility of selection bias against certain polypeptide-surface protein fusions that may occur during construction of high diversity libraries (page 8, line 17, to page 9, line 16). One skilled in the art, given the teachings of the specification, could decide whether the inclusion of one or more copies of a gene encoding a surface protein would be desirable for a particular application.

The Office Action further states that the claimed vectors would also require other elements such as an origin of

replication and at least one selectable marker to permit their propagation in a bacterial host. Applicant respectfully submits that one skilled in the art would understand that an origin of replication and a selectable marker are inherent features of vectors, whether for procaryotic or eukaryotic systems, which need not be explicitly recited in the claims. For example, in Hull et al., Virology, Directory & Dictionary of Animal, Bacterial and Plant Viruses, MacMillan Press Ltd. (1989), provided as Exhibit C, the term "vector," as used in molecular biology, is indicated to mean "a self-replicating DNA molecule into which fragments of DNA can be cloned," which "should contain...one or more selectable feature(s), e.g. antibiotic resistance, distinct plaque formation." Accordingly, Applicants contend that the claims contain all the material elements required for one skilled in the art to make and use the invention.

The Office Action alleges that the specification is only enabling for claims directed to first and second DNA sequences encoding functional portions of the variable heavy and variable light chains of an antibody molecule. The Office Action alleges that a description of primers for other heteromeric binding proteins should have been included in the specification.

The specification teaches that the term "heteromeric receptors" refers to proteins composed of two or more subunits which together exhibit binding activity toward particular molecules, as well as subunit fragments thereof, so long as assembly and function of the assembled complex is retained (page 5, lines 14-19). Heteromeric receptors include, for example,

antibodies and functional fragments thereof, T cell receptors, integrins, hormone receptors and transmitter receptors (page 5, lines 20-23).

The specification teaches that DNA sequences encoding polypeptides of the invention can be obtained using methods known in the art including, for example, cDNA synthesis, PCR or a combination of methods (page 6, lines 18-24). PCR amplification conditions are described by reference to Sakai et al. (page 17, lines 6-7). Exemplary primers for the amplification of Fab antibody sequences are set forth in Tables I and II (pages 17-18). One skilled in the art, given the teachings in the specification and knowledge in the art, could readily have determined appropriate primers to amplify DNA sequences encoding any desired heteromeric subunit sequences.

As corroboration that methods for designing PCR primers and their use for successful amplification of various heteromeric receptors were well known in the art at the time the invention was made, Applicants provide the following references. Choi et al., Proc. Natl. Acad. Sci. 86: 8941-8945 (1989), which is attached as Exhibit D, provides a panel of 22 5' Vβ primers and a 3' Cβ primer for amplification of at least 46 different T cell receptor Vβ regions (see page 8942, Table 1). Oksenberg et al., Nature 345: 344-346 (1990), which is attached as Exhibit E, describes a panel of 18 5' Vα primers, representing the 18 known Vα subfamilies, and a 3' Cα primer for specific amplification of T cell receptor Vα regions (see page 344, Table 1). Scharf et al., attached as Exhibit F, demonstrates specific amplification of sequences from the HLA DQα locus (page 1077, Figure 1, of

Scharf et al., Science 223: 1076-1078 (1986)). All of these references were published prior to the filing of the above-identified application. Similarly, generation of other MHC α and β subunits also was practiced by those skilled in the art (reviewed in Erlich and Bugawan, which is attached as Exhibit G (page 264, Table 1 of Erlich and Bugawan, In PCR Protocols: A Guide to Methods and Applications (Innis et al., eds. 1990)). Therefore, given the teachings in the specification and the state of the art in regard to amplification of known sequences, Applicant contends that one skilled in the art could readily have practiced the invention in connection with any desired heteromeric receptor.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-33 and 66-81 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly incomplete. These rejections have been addressed above in connection with similar rejections under 35 U.S.C. § 112, first paragraph.

Claims 6-8, 22-24 and 31-33 are allegedly confusing because they do not indicate a functional relationship between the recited bacteriophage, the DNA encoding the heteromeric receptors and the cells producing them. Although Applicant maintains that the relationship between the claims is sufficiently clear, the claims have been amended as follows to further prosecution of the above-identified application. Claim 77 has been amended to indicate that the prokaryotic cells of claim 76 produce filamentous bacteriophage. Claim 6 has been

canceled, and claims 7 and 8 have been amended to depend on claim 77. Therefore, Applicants contend that the functional relationship between the bacteriophage, the DNA and the cells in claims 1, 7, 8, 76, 77 is sufficiently clear.

Claim 22 has been amended to indicate that the first and second vectors in the cloning system of claim 16 are filamentous bacteriophage vectors. Claim 31 has been amended to indicate that the expression vectors of claim 26 are filamentous bacteriophage vectors. Claim 32 has been amended to depend on claim 31. Therefore, Applicants contend that the functional relationship between the DNA sequences and the bacteriophage in claims 22-24 and 31-33 are sufficiently clear.

Claim 26 is alleged to be confusing as effectively claiming a plurality of polypeptides forming a single receptor which binds a single molecule. Although Applicant maintains that claim 26 as filed is sufficiently clear, the claim has been amended to further indicate that a plurality of heteromeric receptors is formed, and that at least one of the heteromeric receptors exhibits binding activity toward a preselected molecule. Accordingly, Applicants contend that amended claim 26 and its dependents are sufficiently clear.

Claim 81 is alleged to be vague and indefinite in referring to "possible" first and second DNA sequences. Claim 81 has been canceled as redundant with claim 26. As stated in the previous Response, Applicants contend that the term "possible" in claim 26 is sufficiently clear and definite. The term "possible" means that the claimed plurality of first and second DNA

sequences are the sequences that encode polypeptides which form the plurality of heteromeric receptors. Nevertheless, to further prosecution, claim 26 has been amended and no longer recites the objected term.

Rejections under 35 U.S.C. § 102(b)

Claims 9-14 stand rejected under 35 U.S.C. § 102(b). These claims, directed to a kit for the preparation of vectors for the coexpression of two or more DNA sequences, have been canceled without prejudice in the above-identified application.

Rejections under 35 U.S.C. § 103

Claims 1 to 5 and 25 to 30 remain rejected under 35 U.S.C. § 103 as allegedly obvious over Huse et al., Science 246:1275-1281 (1989), in view of Ladner et al., WO 88/06630 (1988). The Office Action states that the subject of these claims differs from the cells, vectors and cloning system described in the Huse et al. reference in having the receptor protein of the instant invention expressed on the surface of the host cell. The Office Action alleges that the single chain antibodies described by Ladner et al. are encompassed by the polypeptides recited in pending claim 1. More specifically, the Office Action states that a single chain antibody is composed of a first (VH) polypeptide fused to a second (VL) polypeptide in which the two polypeptides are expressed as a fusion protein. The Office Action alleges, therefore, that it would have been obvious to use the surface expression system described by Ladner et al. in a binding protein generation system described by Huse

et al. to reduce the effort required to identify a host organism carrying a DNA sequence encoding a protein having the desired binding characteristics. Applicants respectfully traverse the rejection for the reasons that follow.

The heteromeric receptors of claims 1 and 26 are expressed as a first and a second polypeptide. In other words, the heteromeric receptors are expressed as <u>two</u> polypeptide subunit chains. One (or both) of the polypeptide subunits is fused with a protein that directs expression of that subunit to the cell surface. The other expressed subunit associates with the fusion protein for the assembly of the functional heteromeric receptor at the cell surface (see, for example, page 5, lines 9-11; page 5, lines 17-19; page 5, lines 31-34; page 7, lines 12-13; page 10, lines 26-30). In contrast, a single chain antibody is <u>one</u> polypeptide, which is a fusion between heavy chain and light chain sequences. The specification distinguishes a fusion between two polypeptides to form a single polypeptide, such as a single chain antibody, from the first and second polypeptides of claims 1 and 26, by describing the former as a "linked polypeptide" (page 6, lines 3-10).

Applicant maintains, as stated in the previous Response, that neither Huse et al. nor Ladner et al., alone or in combination, teaches or suggests the expression of two polypeptides which form functional heteromeric receptors or the surface of cells. Huse et al. describes the expression of antibody libraries in lambda phage. Huse et al. does not teach or suggest expression of polypeptides that form heteromeric receptors on the surface of a cell, as taught and claimed by

Applicant. Furthermore, Huse et al. does not provide any motivation for developing libraries of antibodies or heteromeric receptors that assemble on the cell surface. Huse et al. instead states how rapid and easy it is to screen the immunoglobulin libraries described therein (see abstract). The teachings that two heteromeric receptor subunits can be advantageously expressed and assembled at the cell surface for improved screening are found only in the instant application (page 12, line 29, to page 13, line 5).

Ladner et al. describes the expression of single chain antibodies (SCADs). The SCADs described in Ladner et al. are single polypeptides consisting of a heavy chain, a light chain, and a surface protein, such as the gene V protein of lambda phage. The SCADs described in Ladner et al., consisting of one polypeptide, are therefore distinct from the first and second polypeptides that form heteromeric receptors claimed by Applicant. Ladner et al. does not teach or suggest co-expressing two independent polypeptides for their assembly on the surface of a cell to form a heteromeric receptor. The teachings that DNA sequences encoding two independent polypeptides can be combined and expressed at the cell surface are only found in Applicant's specification. Therefore, absent the teachings in the instant application, Ladner et al. provides no suggestion or motivation for expressing diverse combinations of first and second DNA sequences encoding first and second polypeptides which form a heteromeric receptor, as taught and claimed by Applicant. Accordingly, Ladner et al. does not cure the deficiencies of Huse et al.

Therefore, since the expression of two polypeptides that form heteromeric receptors at the surface of a cell is not taught or suggested in either Huse et al. or Ladner et al., one skilled in the art would not have been able to combine the two references to arrive at Applicant's claimed invention. Accordingly, Applicant respectfully requests that this ground of rejection be removed.

Claims 6-8, 22-24 and 31-33 stand rejected as allegedly obvious over Huse et al. and Ladner et al., further in view of Parmley et al., Gene, 73:305-318 (1988). Applicant respectfully traverses the rejection. The Parmley et al. reference describes the use of filamentous phage fusion vectors for the expression of epitope libraries. Parmley et al. does not teach or suggest the use of such vectors to co-express two polypeptide subunits, or to express heteromeric receptor subunits. Therefore, one skilled in the art would not have been able to combine the Parmley et al. references with the Huse et al. and Ladner et al. references to arrive at Applicant's invention.

Claims 1-5 and 25-30 remain rejected as allegedly obvious over Sastry et al., PNAS 86:5728-5732 (1989), in view of Ladner et al. and Robinson et al., WO 87/02671. Claims 6-8, 22-24 and 31-33 remain rejected in view of the above publications, and further in view of Parmley et al. In the previous Office Action it was alleged that the Sastry et al. publication describes the instant invention in its entirety but does not describe its complete reduction to practice. It was further alleged that Ladner et al. and Robinson et al. describe methods to reduce the system of Sastry et al. to practice, and

that motivation to do so can be found in the statement of Parmley and Smith that such methods allow one to "study epitopes on immunologically important proteins without the use of synthetic peptides and without having ever cloned the genes." Applicant respectfully traverses the rejection for the reasons that follow.

Applicant maintains, as stated in the previous Response, that Sastry et al. only describes the cytoplasmic expression of antibody chains. Sastry et al. does not teach or suggest expressing heteromeric receptors on the surface of cells. Robinson et al. describes methods of producing chimeric immunoglobulin molecules. Robinson et al. does not teach or suggest either diverse combinations of DNA sequences encoding immunoglobulin subunits, or any method of expressing two polypeptides that form a heteromeric receptor on the surface of a cell. As described above, Ladner et al. also does not teach or suggest any method of expressing two polypeptides separately as a first and second polypeptide to form a heteromeric receptor on the surface of a cell. The description in Parmley et al. of the applicability of bacteriophage expression for the display of short epitope sequences provides no motivation to use a bacteriophage system for the expression of a first and second polypeptide that form heteromeric receptors.

Therefore, since the expression of two polypeptides that form heteromeric receptors at the surface of a cell was not taught or suggested in Sastry et al., Ladner et al., Robinson et al. or Parmley et al., either alone or in combination, one skilled in the art would not have been able to combine the cited references to arrive at Applicant's claimed invention.

Accordingly, Applicant respectfully requests that this ground for rejection be removed.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. Should the Examiner have any questions, he is invited to call Cathryn Campbell or the undersigned agent.

Respectfully submitted,

Date: 9.21.98

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